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PRINCIPAL INVESTIGATOR: Nola Hylton, Ph.D.

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, California 94143-0962

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Nola Hylton, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, San Francisco
San Francisco, California 94143-0962

e-mail:
nola.hylton@radiology.ucsf.edu

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13. ABSTRACT ***(Maximum 200 Words)***

The goal of this project is the evaluation of a three-point contrast-enhanced magnetic resonance imaging (MRI) technique for characterizing breast carcinoma. We have developed a high resolution method that captures both anatomic heterogeneity as well as differences in contrast uptake pattern, using the signal enhancement ratio (SER). 161 patients have been enrolled to date; 148 of these have had histopathologic correlation. 42 patients with stage III/IV breast cancer underwent pre-operative chemotherapy and received contrast-MRI exams prior to chemotherapy, following 1 cycle, and after completing a full course (4 cycles) of neoadjuvant treatment. We previously reported superior capability of MRI relative to mammography for defining extent of disease in the symptomatic breast, with particular value in cases of multifocal disease or presence of an associated in-situ component. We found a significant correlation between peak SER value and both tumor grade and microvessel density, and demonstrated improved diagnostic specificity of the three-point SER method over a standard two-point 'static' method. Our recent preliminary results in treated tumors demonstrate that contrast-MRI can accurately assess residual tumor volume. Tumor classification by MRI pattern appears to correlate with clinical response and nodal status. MRI may have value for early prediction of end response, recurrence and survival.

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Robert M. Hazlett 1-7-00

PI - Signature Date

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ANNUAL REPORT FOR CONTRACT NUMBER DAMD17-96-C-6126

Project Period September 27, 1998 – September 26, 1999

Principal Investigator: Nola Hylton, Ph.D., University of California, San Francisco

Grant Title: Signal Enhancement Ratios (SERs) in Breast Carcinomas Measured by 3D Contrast-MRI and Verified by Histopathology

INTRODUCTION

Our work in breast MRI has focused on an imaging technique, the **t**riple **a**cquisition **r**apid **g**radient **e**cho **t**echnique (TARGET), and **s**ignal **e**nhancement **r**atio (SER) analysis method, directed toward defining the extent of malignant lesions in patients with confirmed breast carcinoma. We developed a 3-point contrast-MRI method to maximize anatomic (sensitivity) and biologic (specificity) information in a single exam. Previously reported methods have relied on separate imaging strategies for maximizing sensitivity and specificity[1-12].TARGET acquires one data set at baseline (pre-contrast), S_0; one early post-contrast, S_1; and one late post-contrast, S_2. The SER index, defined as $(S_1 - S_0) / (S_2 - S_0)$, compares early to late enhancement: SER values less than one indicate breast tissue that enhances gradually; SER values equal to one indicate breast tissue enhancement that is stable between the early and late post-contrast time points; SER values greater than one indicate breast tissue demonstrating uptake with contrast washout by the late time point[13-15]. In the preliminary data provided in our original grant application, we presented results in a group of 25 patients with pathology confirmation. MRI correctly identified carcinoma in 21/25 cases using a two-point comparison only: percent enhancement (PE) = $(S_1 - S_0)/ S_0 > 80\%$. The one false positive was resolved when SER>1.2 was used as an additional criteria for malignancy. Of particular interest, these preliminary studies also suggested a relationship between SER value and tumor grade in the group of 18 invasive carcinomas. The focus of this grant has been to verify these findings in a larger population of patients with confirmed breast carcinoma, and investigate the potential of SER as a non-invasive prognostic marker.

BODY

Experimental Methods, Assumptions and Procedures: 50 women subjects per year are enrolled in this research protocol and receive one breast MRI exam prior to undergoing surgery. Study eligibility include women with highly suspicious breast abnormality or confirmed breast carcinoma on the basis of fine needle aspiration (FNA), core biopsy, excisional biopsy, or lumpectomy with positive margins. The MRI procedure is performed on a General Electric 1.5 Tesla SIGNA scanner using a bilateral phased-array breast radiofrequency coil. The imaging exam consists of a bilateral, axial T1-weighted, spin echo localization scan, a sagittal, fat-suppressed T2-weighted fast spin echo scan of the symptomatic breast only, and contrast-enhanced TARGET series of the symptomatic breast only, using a 3D fat-suppressed, fast gradient echo sequence: TR = 11 ms, TE = 4.2 ms, 20 degree flip angle, 256 x 192 imaging matrix, 16-18 cm field of view, 60 sections, 2 NEX and no phase wrap option. The scan time for each data acquisition is 5.4 minutes, resulting in a three-point temporal sampling of 0, 2.7 and 8.1 minutes. Gadolinium-DTPA is administered intravenously through an indwelling catheter at a dose of 0.1 mmol/kg body weight, following the first scan of the TARGET series.

Software and hardware upgrades to our General Electric Signa scanner over the past two years have allowed us to decrease the TR of the 3D pulse sequence to 8.0 ms, maintaining all other parameters constant. The resulting scan time is 4:36 minutes, resulting in a new temporal sampling of 0, 2 min 18 sec and 6 min 54 sec.

Following each patient exam, MRI data are transferred off-line to a UNIX workstation for processing and analysis. Maximum intensity projections and region-of-interest calculations are performed to measure peak PE and SER values in the area of suspicion based upon the patient's reason for referral. Additional areas of suspicion and incidental MRI findings are also characterized. Tissue tracking and histopathology correlation procedures were developed in Year I and continue to be used in this study.

Results and Discussion: We have accrued an additional 45 patients into our study. Our combined patient database now includes 386 patient entries. In our Statement of Work, we estimated that Task 5 &6 under Specific Aim 1 would be underway during Year 3, and work on Task 2 under Specific Aim 2 would continue. These tasks were as follows:

SPECIFIC AIM 1 (Determine the histologic basis for interpreting SER patterns)
Task 5: Analyze SER/grade and SER vessel count data; Use results to reclassify SER ranges for improved segmentation. Perform restrospective analysis of studies to date.
Task 6: Perform remaining patient studies; compile results in accumulated studies.

SPECIFIC AIM 2 (Investigate the possible prognostic value of SER characteristics)
Task 2: Perform patient studies; analyze and cmpile SER results for data base. Compile pathology and factor-VIII results. Obtain patient follow-up data.

Our current patient database includes 386 patients with histopathologic results and includes: patient's reason for referral, clinical data, patient history, results of diagnostic tests (mammography, ultrasound, needle biopsy), MRI and pathology. We have performed retrospective evaluations of the effectiveness of contrast-enhanced MRI in several staging applications. We evaluated the diagnostic accuracy of our imaging technique by developing a diagnostic algorithm combining both dynamic and morphologic features of breast lesions on high spatial resolution MRI. In a retrospective sample of 57 patients with suspicious mammographic or palpable findings at the time of MRI, the temporal pattern of enhancement emerged as the most significant MRI imaging parameter by classification and regression tree (CART) analysis, followed by lesion margin. In the population tested, the diagnostic rule yielded a sensitivity and positive predictive value of 97% each and a specificity and negative predictive value of 96% each. The results of this study were recently accepted for publication in the American Journal of Roentgenology[21].

We evaluated the influence of time interval between lumpectomy and MRI on the ability of contrast-MRI to diagnose residual disease. 68 patients in our database underwent MRI following lumpectomy with positive margins. Patients were stratified according to time interval between lumpectomy and MRI. Specificity improved with each additional week of delay. A twenty-eight day interval was recommended to gain diagnostic accuracy while minimizing delay to re-excision: sensitivity and specificity were 86% and 38% respectively in 34 patients scheduled within 28 days following surgery (mean 19 days) versus 93% and 70% in 37 patients scheduled between one and four months (mean 42 days) following surgery. These results were presented at the 85th Scientific Assembly and Annual Meeting of the Radiological Society of North America and were recently submitted for publication[22]. A retrospective analysis is currently underway to evaluate the subset of patients who underwent MRI following a diagnosis of ductal carcinoma in situ (DCIS). This study will evaluate the usefulness of MRI for defining the extent of residual disease and predicting the presence of occult invasive disease, in comparison to mammography.

We have extended our studies to the characterization of tumor response to neoadjuvant chemotherapy. We have enrolled 42 patients with stage III/IV breast cancer who were given neoadjuvant chemotherapy prior to surgery. These patients underwent MRI before and following a complete course (4 cycles) of adriamycin/cytoxan (AC) chemotherapy. In 18 patients, MRI was also performed following the first cycle of chemotherapy to investigate whether early changes measurable by MRI could predict the response at the end of four cycles, or whether there is a correlation between early MRI changes and time

to recurrence and survival. Image analysis is performed by the automated method developed under a previous aim of this grant[20]. Retrospective analysis was performed on a group of 128 benign, in-situ and low and high grade invasive carcinomas. Receiver operating characteristic (ROC) curve analysis was used to optimize SER cutoffs for differentiating benign and malignant lesions, in-situ and invasive cancers, and low and high grade invasive tumors. These cutoffs were used to determine SER ranges for automated tumor segmentation as a method for measuring changes with treatment. Quantitative measurements included tumor volume, peak SER and percent distribution of SER ranges. MRI was found to accurately assess the extent of residual disease. Tumor classification by MRI pattern appears to correlate with clinical response and nodal status. MRI may have value for early prediction of end response, recurrence and survival.

Previous Results (from Years 1 and 2):

We performed a study to evaluate the value of low temporal resolution kinetic information gained by the three-time point method of data acquisition. We compared a two-point method considering PE only to a three-point method combining PE and SER thresholds, for sensitivity and specificity. Thresholds were separately optimized in each case using receiver operating characteristic (ROC) curve analysis and requiring a minimum sensitivity of 95%. A specificity increase from 42 to 67% was found using the three-point method, in comparison to the two-point method. These results will be presented at the RSNA in December 1998 and have been submitted for publication[16].

We evaluated the correlation of SER value and grade, and SER value and microvessel density (MVD) in a group of 57 patients with confirmed carcinoma and subsequent surgical pathology confirmation. SER correlation with microvessel density counts (by CD 34 staining) was highly significant, $r = 0.62$ ($p<0.002$). The correlation between SER and grade (by SBR number) was $r = 0.59$ ($p<0.004$). SER increased with the grade of tumor, showing greatest separation between tumors of grade 2 and 3. These results have been accepted for publication[17-18].

In an evaluation of staging accuracy, tumor extent was measured on MRI and mammography and their concordance with pathology was compared. In a group of 45 patients with carcinoma and MRI and mammography taken at comparable times, carcinoma was correctly identified by MRI in 98% of cases, versus 84% for mammography. True anatomic extent was correctly identified much more often with MRI than with mammography (96% vs. 44%), with the greatest value in cases of multi-focal disease, ductal carcinoma in situ (DCIS), or invasive carcinoma with an extensive intraductal component (EIC)[19].

Key Research Accomplishments during year III:

- Completed development and retrospective testing of a diagnostic algorithm based on the TARGET/SER imaging method. The results have been accepted for publication in the American Journal of Roentgenology[21].
- Completed a study of the impact of time interval between lumpectomy and MRI on the evaluation of residual disease. The results of this study were accepted for presentation at the 1999 scientific assembly of the RSNA and were also submitted for publication[22].
- We have expanded our applications to include quantitative measurements of tumor response to neoadjuvant chemotherapy in locally-advanced breast cancer. Our preliminary results were accepted for presentation at the 22nd Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, 1998. We are in the planning stages for a multi-center trial to evaluate contrast-MRI for assessing response and predicting outcome in patients with stage III breast cancer enrolled in a randomized clinical trial of AC chemotherapy with and without herceptin (preliminary approval for funding by the American College of Radiology Imaging Network (ACRIN).

Reportable Outcomes:

- *Papers:*

  Hylton NM, Kinkel K. *Technical Aspects of Breast Magnetic Resonance Imaging*. Topics Magn Reson Imag. 1998; 9;2;1-14.

  Esserman LJ, **Hylton NM**, Yassa L, Frankel S and Weidner N. *Utility of MRI in the management of breast cancer: evidence for improved preoperative staging.* J Clin Oncol, 1999, 17:1:110-119.

  Esserman LJ, **Hylton NM**, George T and Weidner N. Contrast-enhanced magnetic resonance imaging to assess tumor histopathology and angiogenesis in breast cancer. The Breast Journal, 1999; 5:1:13-21.

  Hylton NM. Vascularity assessment of breast lesions with gadolinium-enhanced MR imaging. MRI Clinics of North America, 1999; 7:2:411-420.

  Hylton NM, Esserman LJ, Partridge SC, Schwerin EH, Wang WL, Weidner N, Barclay J, Sickles EA. High spatial resolution breast MRI: improved specificity using a three-point estimate of contrast kinetics (submitted)

  Kinkel K, Helbich TH, Esserman LJ, Barclay J, Schwerin EH, Sickles EA, **Hylton NM**. Characterization of suspicious breast lesions: diagnostic criteria and interobserver variability in dynamic high spatial resolution MR imaging of the breast (accepted for publication, American Journal of Roentgenology)

  Frei K, Kinkel K, Bonel HM, Lu Y, Barclay J, Esserman LJ, **Hylton NM**. Performance of breast MR imaging in patients with positive margins after lumpectomy: influence of time interval between lumpectomy and MR imaging (submitted to American Journal of Roentgenology)

- Abstracts and Presentations:

  Hylton NM, Esserman LJ, Partridge SC, Wang WL, Schwerin E and Sickles E. Increased Diagnostic Specificity of High Resolution Breast MRI Using a Three-Time-Point Method. Proc. 21st Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, 1998.

  Hylton NM, Esserman LJ, Partridge SC, Wang WL, Kinkel K, Sickles EA. Triple Acquisition Method for Improved Specificity of High Resolution Breast MRI. Radiology 1998; 209(P):468.

  Partridge S, Esserman LJ, Heumann E, Tripathy D and **Hylton NM**. 'Validation of a Semi-Automated Breast MRI Analysis Technique for Tumor Diagnosis and Evaluation of Response to Therapy' 7th Scientific Meeting of the International Society of Magnetic Resonance in Medicine,1999, 2170.

  Frei K, Kinkel K, Bonel HM, Lu Y, Barclay J, Esserman LJ, **Hylton NM**. Performance of breast MR imaging in patients with positive margins after lumpectomy: influence of time interval between lumpectomy and MR imaging. 85th Scientific Assembly and Annual Meeting of the Radiological Society of North America. 1999.

  Hylton NM. Measuring Vascularity With Contrast-enhanced MRI for Tumor Characterization and Staging in Breast Cancer, Workshop on Magnetic Resonance in Experimental and Clinical Cancer Research, International Society for Magnetic Resonance in Medicine, St. Louis, Missouri, November 13-15, 1998

- Funding based on work supported by this award:

The Susan G. Komen Breast Cancer Foundation Jan 2000-Dec 2001
'Magnetic Resonance Imaging and Directed Fine Needle Aspiration Biopsy for High Risk Screening and Surveillance'
Principal Investigator: **N. Hylton**
Total Costs: $248,420.00
Percent Effort: 10%
Study Aim: The goal of this project is to develop and evaluate a magnetic resonance imaging (MRI) screening examination that includes high resolution, fat-suppressed 3D imaging to identify lesions, and MRI-directed fine needle aspiration biopsy (FNAb) to increase diagnostic accuracy.

U.S. Army Medical Research and Materiel Command Oct 1997-Sept 2000
"Improving the Specificity of High Resolution Breast MRI by Optimizing Data Acquisition Techniques and Diagnostic Models"
Principal Investigator: Savannah Partridge
Role on Project (N. Hylton): Faculty Mentor
Percent Effort: 5%
Total Costs: $42,206.00
Study Aim: To develop and optimize new diagnostic models for high resolution 3D contrast MRI of the breast for improved differentiation between benign and malignant breast.

CONCLUSIONS

We have continued to evaluate the value of high resolution contrast-enhanced MRI for pre-surgical staging, assessment of treatment response and non-invasive prognosis. We are retrospectively analyzing the performance of our contrast-MRI for multiple staging applications, including the effects of time delay following lumpectomy on the evaluation of residual disease following MRI, and the usefulness of contrast-MRI in defining residual disease, detecting occult invasion in patients with a biopsy demonstrating DCIS only. We have extended our studies to the application of quantitative MRI to the assessment of tumor response to chemotherapy and we are investigating the predictive value of early treatment changes measured by MRI.

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